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A comparison of the crystal packing in benzene with the geometry seen in crystalline cyclophane–benzene complexes: guidelines for rational receptor design

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Self-recognition in crystalline benzene is compared with the recognition of benzene in inclusion complexes of three cyclophane receptors. It is shown that the structural organization of aromatic rings, which determines the packing in the molecular crystal and the binding geometry in the preorganized cavity of the cyclophane host molecules, follows the same principles. It is concluded that the examination of the spatial requirements of the aromatic–aromatic interaction motifs found in crystals should allow one to design host bonding skeletons with high binding selectivity and affinity for a specific aromatic guest.

1. Introduction

X-ray crystallography is a central method in molecular recognition studies to provide accurate information on the structures of molecular complexes and the nature of the non-bonded interactions between the binding partners. In an increasing number of studies, interactions between aromatic rings are found to profoundly influence host–guest binding geometries (Jazwinski et al. 1987; Hamilton 1990; Diederich 1991; Whitlock & Whitlock, 1990), and thermodynamic analysis in solution confirms that these interactions provide significant stabilization to the complexes (Williams et al. 1989; Smithrud et al. 1991; Zimmerman & Wu 1989). Aromatic–aromatic interaction modes in host–guest crystals occur mainly between two extremes, a π–π stacking of parallel-shifted aromatic rings (Hunter & Sanders 1990) and a T-shaped or 'edge-to-face' interaction mode in which C–H bond dipoles at the rim of one ring are oriented toward the negatively charged carbons of the second ring. Benzene forms a T-shaped dimer in the gas phase (Janda et al. 1975; Steed et al. 1979) and computational studies also indicate a preference for the T-shaped dimer geometry in pure liquid phase as well as in water and chloroform solutions (Jorgensen & Severance 1990). The T-shaped interactions also dominates the structure of crystalline benzene (Bacon et al. 1964; Piermarini et al. 1969), and this will be discussed below in greater detail. In crystals of polycyclic aromatic hydrocarbons (PAHs), the ratio of C...C to C...HC contacts governs the crystal packing pattern (Gavezzotti 1989; Gavezzotti & Desiraju 1988; Desiraju & Gavezzotti 1989). Smaller derivatives like benzene or naphthalene prefer the edge-to-
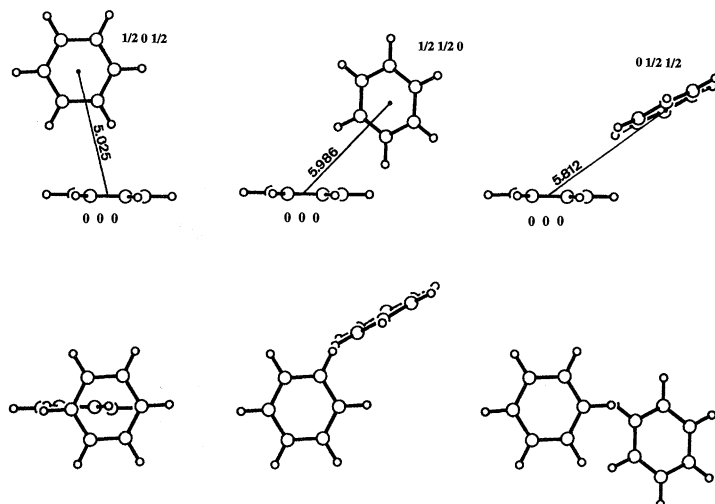
Figure 1. Two orthogonal views (upper and lower rows) of the basic next-neighbour motifs in crystalline benzene (P*bca*); left: pairing approximating the ideal edge-to-face orientation in the gas phase dimer (centre-to-centre distance 5.025 Å, rings located at 0, 0, 0 and 1/2, 0, 1/2 in the unit cell); centre: dimer with perpendicular arrangement but a larger offset (5.986 Å, rings at 0, 0, 0 and 1/2, 1/2, 0); right: pairing with inclined ring moieties (5.812 Å, rings at 0, 0, 0 and 0, 1/2, 1/2). The corresponding interplanar angles are given in table 1.

face association leading to a pure herringbone packing missing any stacking of next-neighbouring molecules. For the larger aromatic hydrocarbons with a decreasing ratio of C...C to C...HC contacts such as pyrene, coronene, and kekulene (Staab *et al.* 1983), herringbone packing of parallel stacked dimers or infinite stacks with parallel translated molecules is observed. The latter examples are increasingly stabilized by substantial van der Waals forces as a result of the π–π interactions between the parallel-shifted extended aromatic surfaces. Optimal π–π stacking at an intermolecular distance of 3.35 Å occurs in graphite, with its infinite C...C to C...HC ratio. Finally, π–π stacking and edge-to-face interactions also dominate the packing of aromatic rings in thousands of other observed crystal structures including those of proteins (Burley & Petsko 1986, 1988).

　In this paper, we compare self-recognition in crystalline benzene with the recognition of benzene in complexes of cyclophane receptors and explore the similarities and differences that benzene encounters in the two different environments. Specially, we ask the question whether the examination of the structures of crystalline guest, in this case benzene, could provide useful guidance for rational host design. To answer this question, the supposed similarities between aromatic–aromatic interactions determining the molecular packing in infinite benzene crystals and the interactions defining recognition and organization in molecular cyclophane–benzene complexes, are inspected more closely. A convincing example for the design of an elegant supramolecular system, that has been largely guided by X-crystal structure analysis, is the development of a [2]catenane by Stoddart and co-workers (Ortholand *et al.* 1989; Ashton *et al.* 1989).

2. Results and Discussion

For the comparison between the packing of benzene in its crystal and in host–guest complexes, three cyclophane–benzene complexes with varying orientations of the substrate were chosen. In 1985, Krieger & Diederich published the molecular and crystal structure of **1**. 2-benzene monohydrate (**2**) which shows one benzene ring perfectly enclosed within the intramolecular cavity of cyclophane **1** whereas a second benzene ring is located in a channel type intermolecular cavity of the crystal lattice. In the same year, Saigo *et al.* (1985, 1986) reported that cyclophane **3** forms a crystalline 1:1 complex (**4**) with benzene, and the X-ray crystal structure analysis showed that the guest is located between two host molecules. Later, Brown *et al.* (1989) found that the hexaoxacyclophane **5** forms a 1:1 molecular complex (**6**) in which benzene is encapsulated in the macrocyclic cavity.

1
2 = Complex **1** · 2 C_6H_6 · H_2O

3
4 = Complex **3** · C_6H_6

5
6 = Complex **5** · C_6H_6
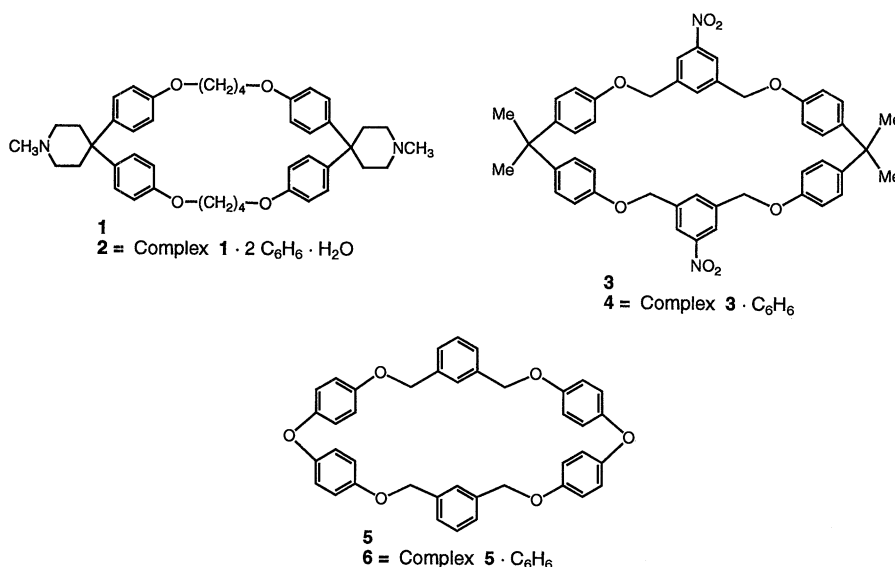
Benzene crystallizes in the orthorhombic space group P*bca* ($a = 7.39$, $b = 9.42$, $c = 6.81$ Å; Bacon *et al.* 1964) with four molecules in the unit cell positioned on inversion points that are located at face centres of the cell (a high pressure phase in $P2_1/c$ is also known (Piermarini *et al.* 1969). Next-neighbour molecules are related along the three lattice directions by 2_1 screw axes and glide planes. Each molecule is surrounded by 12 next-neighbours which arrange in three different groups corresponding to the three screw axes. In the first group (figure 1, left), benzene molecules pack edge-to-face with a centre-to-centre distance of 5.025 Å; an example for this relation is given by the pair centred at the origin (0, 0, 0) and at (1/2, 0, 1/2) (table 1). Two adjacent CH-bonds of the first molecule point toward the core of the neighbouring benzene molecule, and a shift of the centre of the first from the normal centred on the second molecule is observed so that one hydrogen of the first is located above the centre of the second molecule. This geometry approximates the ideal edge-to-face or T-shape orientation in the gas phase dimer; it is estimated to be about 16 % less favourable in energy compared with the ideal situation (Williams & Xiao 1993). In the second group (e.g. 0, 0, 0 ↔ 1/2, 1/2, 0), a larger centre-to-centre distance is found (figure 1, centre, table 1). Again the neighbouring aromatic rings adopt nearly perpendicular orientation, with a more pronounced offset from the normal direction.
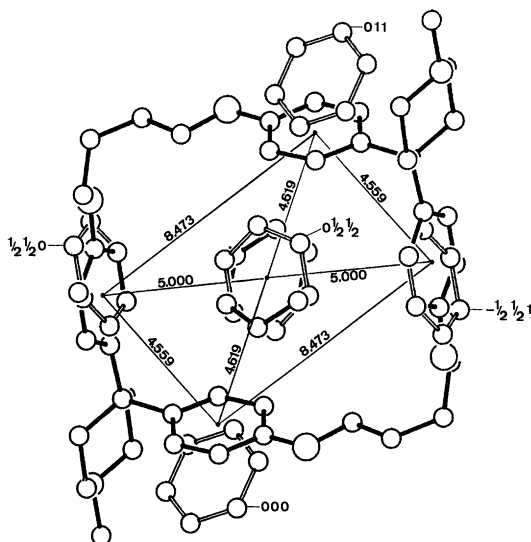
Figure 2. Superimposition of a subset from the packing of crystalline benzene (empty bonds, classified by their centring in the crystal packing) with the molecular structure of **2** in the crystal (solid bonds), mutual centre-to-centre distances between the aromatic rings in the host are given, corresponding interplanar angles are listed in table 2.

Table 1. *Centre-to-centre distances and mutual interplanar angles in crystalline benzene*

(Benzene structure: $a = 7.390$, $b = 9.420$, $c = 6.810$ Å, *Pbca*. The different rings are classified by the centres at which they are located in the crystal (0, 0, 0: origin, 1/2, 1/2, 0: *ab*-face centred, 1/2, 0, 1/2: *ac*-face centred, 0, 1/2, 1/2: *bc*-face centred. Distances (first row) are in Å, angles (second row) are in degrees.)

	0, 0, 0	1/2, 1/2, 0	1/2, 0, 1/2	0, 1/2, 1/2
0, 0, 0	—	5.986	5.025	5.812
		86.1	86.5	29.4
1/2, 1/2, 0		—	5.812	5.025
			29.4	86.5
1/2, 0, 1/2			—	5.986
				86.1

One benzene molecule is oriented with one of its CH bonds toward the plane of the other ring. In the third group (figure 1, right), the planes through aromatic rings of neighbouring molecules (e.g. 0, 0, 0 ↔ 0, 1/2, 1/2) are inclined by only *ca.* 30° and two CH bonds are approximately oriented toward the core of the neighbouring benzene ring. The latter two next-neighbouring pairings contribute less to the interaction energy (Williams & Xiao 1993).

The packing of crystalline benzene was matched onto the crystal structure of the cyclophane–benzene inclusion complex **2** (figure 2). In a least-squares super-imposition, the four aromatic rings of the two diphenylmethane units were matched onto benzene molecules centred at 0, 0, 0 and 1/2, 1/2, 0 or 0, 1, 1 and −1/2, 1/2, 1, respectively, in crystalline benzene (figure 2, empty bonds). Mutual centre-to-centre distances between the aromatic rings in the host skeleton (solid bonds) are given, and the corresponding interplanar angles are listed in table 2. Based on the centres of the according aromatic rings in the host and in crystalline benzene, an RMS-derivation of
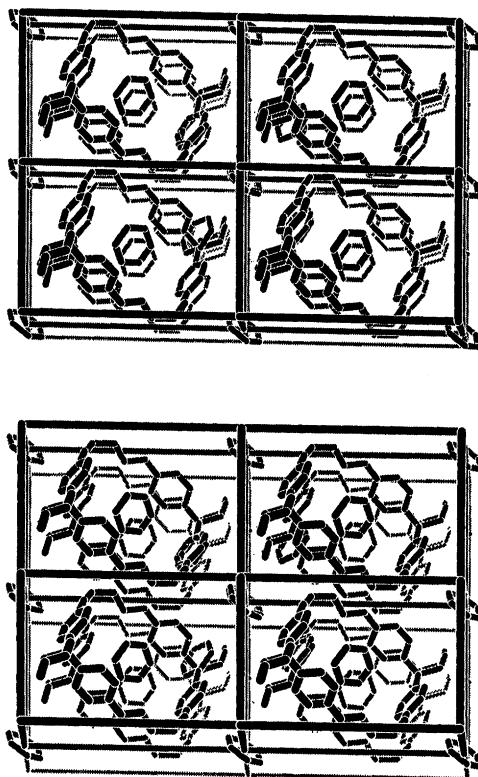
Figure 3. Stereodiagram of the crystal packing of **2** showing the next-neighbour environment of the 'guest' and the 'clathrate-type' benzene molecule. Superimposed to the central clathrate benzene is a section from a packing in crystalline benzene to demonstrate the equivalent edge-to-face pairing and the spatial correspondences of the piperidine moieties with two additional rings from the benzene packing.

Table 2. *Centre-to-centre distances and mutual interplanar angles in the crystal structure of* **2**

(The different rings are classified by the notation used in the benzene packing for the ring centres being equivalent to portions in the host–guest complex. The obtained correspondences are given by the centre-to-centre distances shown in figure 2. Distances (first row) are in Å, angles (second row) are in degrees.)

	0, 0, 0	1/2, 1/2, 0	1/2, 0, 1/2	0, 1/2, 1/2
0, 0, 0	—	4.559	—	4.619
		85.2		40.3
1/2, 1/2, 0		—	—	5.000
				78.9
1/2, 0, 1/2			—	—

0.96 Å is achieved. As a result of this matching, the position of the guest benzene molecule coincides closely with the benzene ring centred at 0, 1/2, 1/2 in the packing of crystalline benzene. The centres of both rings are exactly superimposed due to symmetry, **2** being centrosymmetric. Best planes calculated through the atoms of the two rings include an angle of 28.8°, and the two rings are only slightly (6°) rotated against each other.

A comparison of the centre-to-centre distances and interplanar angles in this
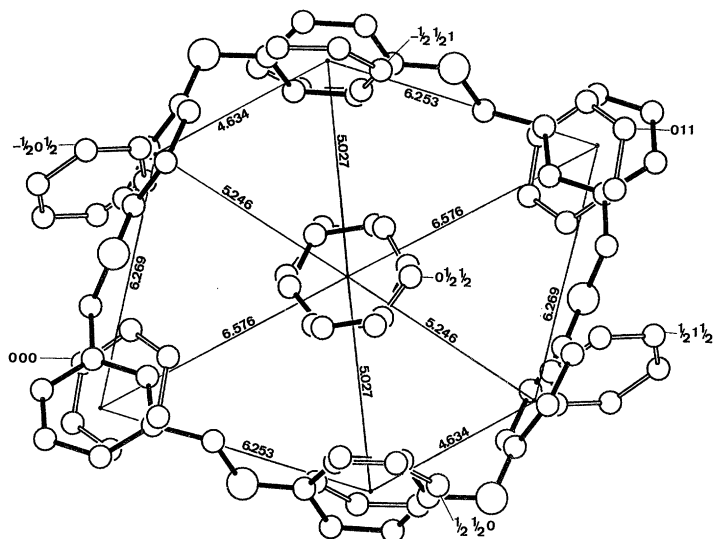
Figure 4. Superimposition of a subset from the packing of crystalline benzene (empty bonds, classified by their centring in the crystal packing) with the molecular structure of **6** in the crystal (solid bonds), mutual centre-to-centre distances between aromatic rings in the host are given, corresponding interplanar angles are listed in table 3.

complex with equivalent ones in benzene shows that the most favourable edge-to-face interaction is best preserved in this complex. The other two contact pairs in the complex show slightly shorter distances, perhaps, because the restrained bonding skeleton of the host reinforces a somewhat more 'compressed' packing.

A second benzene molecule is present in the crystal structure of **2** forming a clathrate-type structure with the complex. The analysis of the next-neighbour relations for this ring shows that two favourable edge-to-face pairings from crystalline benzene are well conserved in its environment (centre-to-centre distance: 5.049 Å, interplanar angle: 80.0°). Two piperidine moieties of the host fall close to the positions occupied by additional benzene molecules in crystalline benzene. However, additional next-neighbour contacts, structurally related to the packing in benzene, are not found. In addition, water has been co-crystallized with this complex forming hydrogen bonds with the basic nitrogen of the piperidine moieties (Krieger & Diederich 1985). In figure 3, the packing of the complex in P$\bar{1}$ is shown, superimposed with five rings from the packing in benzene. The comparison between the environments of the two different benzenes in **2** clearly shows that the intra-cavity guest which according to studies with cyclophanes closely related to **1**, is bound in solution in an enthalpy-driven process (Ferguson *et al.* 1991; Jorgensen & Nguyen 1993), preserves more of the basic packing motifs of crystalline benzene than the second, extra-cavity benzene that only undergoes clathrate formation.

In the crystal structure of cyclophane complex **6** (figure 4), six phenyl rings surround one benzene guest molecule (Brown *et al.* 1989). According to the previous example, a subset of the benzene packing has been matched onto the six phenyl moieties of host **5**. For the superimposition, benzene molecules centred at 0, 0, 0; 1/2, 1/2, 0; 1/2, 1, 1/2; 0, 1, 1; −1/2, 1/2, 1, and −1/2, 0, 1/2 have been used and, with respect to the centres of the six rings, an rms-deviation of 0.82 Å is achieved. As in the previous example, the centres of the guest moiety and a molecule from crystalline

Table 3. *Centre-to-centre distances and mutual interplanar angles in the crystal structure of* **6**

(The different rings are classified by the notation used in the benzene packing for the ring centres being equivalent or translationally equivalent to portions in the host–guest complex (e.g. $-1/2, 0, 1/2$ corresponds to $1/2, 0, 1/2$ by a translation of one unit cell along the negative a-axis. The obtained correspondences are given by the centre-to-centre distances shown in figure 4. Distances (first row) are in Å, angles (second row) are in degrees.)

	0, 0, 0	1/2, 1/2, 0	1/2, 0, 1/2	0, 1/2, 1/2
0, 0, 0	—	6.253	6.269	6.576
		55.9	88.7	11.6
1/2, 1/2, 0		—	4.634	5.027
			74.1	55.3
1/2, 0, 1/2			—	5.246
				78.4

benzene, centred at 0, 1/2, 1/2, coincide exactly due to the centrosymmetry of **6**. Best planes through these two rings enclose an angle of 26.3°. Only a slight mutual rotation of the rings is observed. Comparing the centre-to-centre distances and interplanar angles (figure 4, table 3), with the corresponding ones in benzene, larger deviations are revealed as in the previous case. The edge-to-face pairing in benzene (5.025 Å, 86.5°, figure 1, left) formally corresponds to the contact pairs with centre-to-centre distances of 5.027 and 6.269 Å in **6**. Whereas the closer pair deviates substantially from a perpendicular arrangement, the second conserves this approach direction. Similar observations hold for the more distal pair in benzene with perpendicular approach geometry (table 3). The third pairing motif in benzene with inclined rings is only roughly conserved in this host-guest complex. In total, the centres of the aromatic rings of cyclophane **5** and the guest in complex **6** compare convincingly with equivalent positions in crystalline benzene, however, considerable orientational distortions of the ring planes are observed. Supposingly, these perturbations arise from conformational constraints of the host skeleton. Nevertheless, it is likely that the packing pattern, established in benzene, and which exhibits an optimal situation for a molecule with these recognition capabilities, still influences the structural organization of host **5** and the non-bonded interactions in complex **6**.

Complex **4** represents a third example, also showing six phenyl rings of a cyclophane (**3**) coordinating to one benzene guest molecule, that has been compared with the packing arrangement in solid benzene (Saigo *et al.* 1985). In the crystal structure of this complex, the benzene guest is slightly displaced from a best plane formed by the centres of the aromatic rings of the host skeleton which adopts a chair-like conformation. Accordingly, this structure can be looked at as an intermediate between a host–guest inclusion complex and a clathrate structure. Compared with the situation of the intra-cavity benzene in the crystal structure of **2** (figure 2), a reduced affinity of benzene toward host **3** is to be expected. Accordingly, whereas cyclophane **1** (as quaternary ammonium derivative) binds benzene in aqueous solution (Diederich *et al.* 1985), no evidence for 1 : 1 host–guest complexation by **3** in solution has been reported (Saigo *et al.* 1985, 1986). Nevertheless, packing motifs from crystalline benzene can still be detected in the structural organization of this complex. The centres of the molecules in benzene, used for superimposition, are classified in figure 5. An RMS-deviation of 0.86 Å has been achieved and corresponding

Figure 5. Superimposition of a subset from the packing of crystalline benzene (empty bonds, classified by their centring in the crystal packing) with the molecular structure of **4** in the crystal (solid bonds), mutual centre-to-centre distances between aromatic rings in the host are given, corresponding interplanar angles are listed in table 4.

Table 4. *Centre-to-centre distances and mutual interplanar angles in the crystal structure of* **4**

(The different rings are classified by the notation used in the benzene packing for the ring centres being equivalent or translationally equivalent (e.g. -1/2, 1/2, 0 corresponds to 1/2, 1/2 0) to portions in the host–guest complex. The obtained correspondences are given by the centre-to-centre distances shown in figure 5. Distances (first row) are in Å, angles (second row) are in degrees.)

	0, 0, 0	1/2, 1/2, 0	1/2, 0, 1/2	0, 1/2, 1/2
0, 0, 0	—	4.799	5.215	5.174
		89.1	89.5	52.5
1/2, 1/2, 0		—	6.330	5.054
			6.4	66.7
1/2, 0, 1/2			—	5.900
				61.8

centre-to-centre distances and interplanar angles are given in the figure and in table 4. A closer examination of the molecular packing (figure 6) of complex **4** in P1̄ shows that the guest molecule is actually coordinated in the crystal environmental from either sides by two neighbouring host molecules that are translationally related. Interestingly enough, for this packing host dimer, that encapsulates the guest molecule entirely, a relation to the packing motif in crystalline benzene is obvious. As shown in figure 6, six of the neighbouring benzene rings come from the host molecule which includes the guest partially in its cavity (intra-complex coordination) and the coordination sphere of the guest is completed 'intermolecularly' by the next-neighbouring host through crystal packing. Compared to the 'inner' coordination sphere with 12-next-neighbours in crystalline benzene (shown in figure 7) 10 of these contacts are approximately preserved whereas for the two remaining ones (indicated by arrows in figure 7), no equivalences are present in the crystalline host–guest dimer. The two additional rings being part of the two coordinating host skeletons (cf.
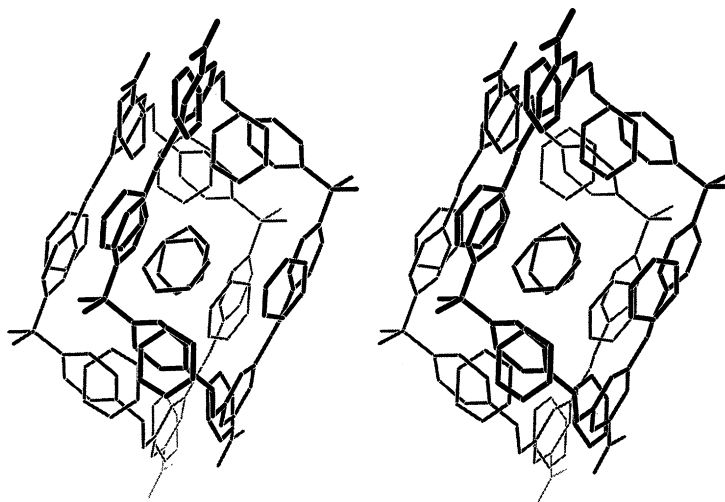
Figure 6. Stereodiagram of the packing host dimer in crystalline **4**, which encapsulates a molecule of benzene, superimposed with a subset from the packing in crystalline benzene. The 12 phenyl portions of two neighbouring hosts coordinate the 'guest' benzene, and a spatial correspondence to the location of benzene moieties in the packing of crystalline benzene can be established.
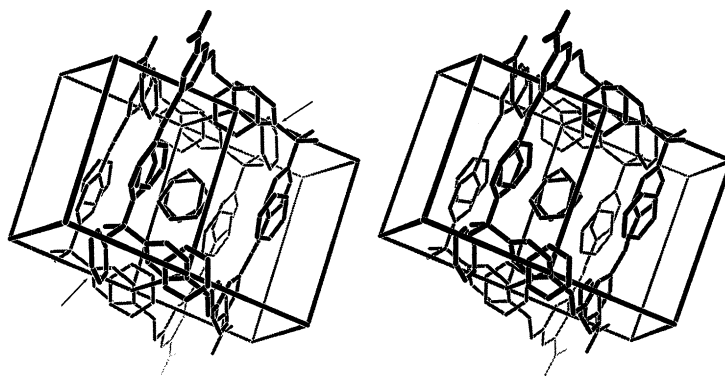

Figure 7. Stereodiagram of the superimposed inner coordination sphere in crystalline benzene with a packing host dimer in **4**, encapsulating a benzene molecule. 10 of the 12 next-neighbours contacts in benzene are approximately preserved in the host dimer-benzene structure, only two moieties (arrows) do not find appropriate equivalences.

figure 5, ring with centre-to-centre distance of 8.728 Å) find their correspondences in members of the 'second' coordination sphere in crystalline benzene. The analysis of the crystal packing of **4** in comparison to the structure of crystalline benzene leads to an interesting and promising challenge for synthetically skilled practitioners in molecular recognition. By constructing a covalently linked double-decker cyclophane derived from two entities of **3**, a receptor should become available, which fully encapsulates benzene and provides 10 or more of the nearest-neighbour aromatic–aromatic interactions of a benzene molecule in crystalline benzene. Such a receptor should show particularly high binding selectivity and affinity for benzene as guest.

3. Conclusions

The final example demonstrates convincingly that the structural organization of aromatic rings, whether one considers the packing in a molecular crystal or the binding geometry in the preorganized cavity of a cyclophane host molecule, follows the same principles if the energetics of other structure-determining terms, such as the conformations of the cyclophane bridges are not unfavourably affected. Examining precisely the spatial characteristics of aromatic–aromatic interaction motifs in solid state packings allows one to design host bonding skeletons with better tailored geometry and higher selectivity and affinity toward specific aromatic guests. A similar examination certainly should also be rewarding and generate useful guidelines for receptor design if other intermolecular forces such as hydrogen-bonding or ion-pairing determine the crystal packing (Hagler & Leiserowitz 1983; Etter 1990; Garcia-Tellado *et al*. 1991). This conclusion implies that a produced crystal environment is of high selectivity and specificity for the species being crystallized. Several observations support this assumption. In general, crystals of one single compound are obtained from a solution containing several components. The formation of binary or ternary crystalline systems as a mixture of different equally-sized compounds appears to be more the exception. Disorder and polymorphism are rather frequently observed in solid state structures. In the first case, only substitutional disorder is relevant, i.e. a given site is occupied at random in different unit cells by two or more types or groups of atoms. This type of disorder is rather rare in organic materials. Nevertheless, it demonstrates which molecular portions possess closely related recognition capabilities. Polymorphism shows that molecules can pack in various ways to achieve energetically favourable arrangements ('local' energy minima). Which of these is finally produced under any given conditions depends, besides a free energy balance, strongly on kinetic effects. However, Gavezzotti & Desiraju (1988) conclude from the analysis of polymorphs of aromatic hydrocarbons that the overall packing patterns do not change in these polymorphs. This fact underlines the importance of particular interaction motifs in mutual recognition and formation of molecular assemblies. Etter (1990) has shown that hydrogen-bonding patterns in crystalline systems can be classified by sets of recurring basic motifs. The statistical analysis of non-bonded contacts around common functional groups reveals patterns which exhibit distinct orientational preferences for the different groups (Murray-Rust & Glusker 1984; Klebe 1993). Systematic studies on crystalline phases formed between different but structurally related species are still rather limited. However, they should allow important insight into the principles underlying the mutual recognition of molecules. If we assume that the features important for recognition can be related to some basic packing motifs, e.g. exhibited in the solid state as shown in the present study for aromatic–aromatic interactions, then any rational design process of specific hosts in supramolecular chemistry or of ligands in protein-receptor complexes has to regard these principles to achieve selectivity.

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